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There is substantial evidence to suggest that estrogens play a key role in the etiology of breast cancer. Both cross-sectional studies of highly trained athletes and prospective studies of high intensity exercise training programs have found a higher frequency of anovulation, lower levels of estradiol and in some cases a shortened luteal phase length with associated lower estradiol levels among these women. However, little is known about the effects of *moderate intensity* exercise on ovarian function. We hypothesize that the observed reduction in risk with exercise is due to altered ovarian function. We are investigating the relationship between a *moderate intensity* exercise training program and ovarian function. Specifically we aim: 1) to determine whether changes occur in frequency of ovulation as a result of a 6 month exercise training program, 2) to determine whether changes occur in serum E_2 levels in ovulatory and anovulatory cycles in these women, and 3) to determine the luteal phase menstrual cycle lengths of these women as a result of the training program.

We are collecting blood and urine specimens and questionnaire data (over a three year period) from 120 premenopausal women. We expect to have completed data and preliminary findings on 39 women by December 1997.

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Lisa S. Thomas 9/28/97

PI - Signature Date

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The Effect of a Moderate Aerobic Exercise Training Program on Ovarian Function
Annual Report (Year 1)

INTRODUCTION

Breast cancer is the most common serious cancer occurring in American women. As a cause of death among women, breast cancer ranks second only to lung cancer [1]. On the basis of current incidence rates, one in nine women will be diagnosed with breast cancer in her lifetime [1].

There is substantial experimental, clinical and epidemiological evidence that ovarian hormones, particularly estrogens, play a major role in breast cancer risk. These studies have shown that lower levels of estrogen are associated with a reduced risk of disease [2,3].

The study proposed here will generate new information about the influence of exercise on ovarian function in non-athletes. By beginning the process of establishing how much exercise is needed to reduce estrogen levels, we hope to be able to provide practical advice to women on how to reduce their breast cancer risk.

Hormones and breast cancer risk:

A great deal of evidence exists demonstrating that ovarian hormones, in particular estrogens, play a major role in breast cancer risk [1-3]. The age-incidence relationship of the common non-hormone related cancers such as stomach and bladder shows a continuous steady increase with age. In contrast, breast cancer incidence increases steadily and rapidly with age until about age 50 (average age at menopause) at which time the rate of increase slows dramatically [2]. Direct epidemiological study of the effect of age at menopause shows that for each year a woman's ovaries continue to function there is a 10% increase in her subsequent breast cancer risk [1, 2, 4]; this is true whether the menopause is natural or artificial (bilateral oophorectomy). The decline in the rate of increase in incidence around age 50 is thus directly correlated with the markedly reduced serum levels of estrogen (and progesterone) after menopause.

Ovulating women in low breast cancer risk Asian countries have been shown to have lower levels of circulating estrogens that women in the US and the UK, both high risk countries [5]. Postmenopausal breast cancer cases have been found to have higher serum estrogen levels than controls [3]. Although initial reports were inconclusive, recent studies, which paid strict attention to factors which may influence hormone levels in cases, found statistically significant elevated serum levels of estradiol in premenopausal breast cases compared to controls [5].

Estrogen is presumed to increase risk of breast cancer through its known action as a breast cell mitogen [2]. Higher levels of endogenous estrogen would be expected to increase mitotic activity. Both follicular and luteal phase estradiol (E2) are of interest; the breast cell proliferation rate in the follicular phase is some 50% that in the luteal phase and so E2 levels in both phases are important [2]. There is evident, though controversial, that progesterone (Prg) also acts to increase breast cell proliferation. We are making measurements of both E2 and Prg.

Exercise and breast cancer risk:

A survey of surviving Harvard female college athletes found that the athletes had a 46% reduction in prevalence of breast cancer compared to non-athletes (24/2622 vs. 45/2776; 2 sided P=0.05) [6]. A Finnish cohort study showed that physical education teachers had an age-adjusted 19% lower risk of breast cancer than language teachers, but the results were not statistically significant (22/924 vs. 106/3239; 2-sided P=0.21) [7]. The NHANES I cohort was reported as showing no overall relationship between exercise levels and breast cancer risk, but the questions asking about exercise activity had no duration component and the study has to be considered non-informative [8].

We recently completed a case-control study of 545 young (age 40 or younger) breast cancer cases and 545 control women matched for age, race, parity and neighborhood of residence [9]. The daily average lifetime (post menarche) number of hours spent in exercise activities was a significant predictor of reduced breast cancer risk (2-sided P<0.0001). Compared to inactive women, risk of breast cancer was reduced by 27% in women who exercised on average 2.5 hours per week, and was reduced by 58% in women who exercising 4 or more hours per week (average approximately 60 mins/day).

Exercise and reproductive function:

We believe, based on our understanding of the relation of ovarian hormones to breast cancer risk [2,3], that the observed protective effect of exercise against breast cancer is likely to be due to a reduction in exposure to serum estrogen. Reduced serum estrogen levels may be due to an increased frequency of anovulatory cycles and/or to decreased circulating levels of estrogen in ovulatory cycles. E2 is the most important estrogen and we will concentrate our attention on E2 in this proposal [2,3]. Cycles with long follicular phase will be associated with lower than average cumulative E2 exposure since such cycles have an increased number of days with early follicular phase low E2 levels. Cycles with short luteal phases have also been found to be associated with low E2 values [10].

Training Studies:

Except for a study by Shangold et al. [11] on a single individual, the studies discussed above compared groups of women who were self selected on exercise level. Some or all of the effects may, therefore, be due to other aspects of their lifestyles or to genetic factors that are strongly correlated with exercise activity, particularly diet. Furthermore, the validity of self-reported responses in cross-sectional studies are of great concern. The potential strength of this prospective training study lies in the ability to structure and monitor the type, intensity and duration of exercise without having to rely on second-hand reports.

We have identified only four exercise training studies of exercise and ovarian function under a controlled protocol which included pre- and post-training testing, all were conducted using very few subjects. The first of these studies was conducted by Boyden et al. [12] among 19 women who had previously engaged in informal running (average, 15.1 mi/wk) and were trained rigorously to run a full marathon over a 14 to 15 month period. Each subject had blood samples taken at baseline, after their weekly mileage had increased by 30 miles per week and again when weekly mileage had increased by 50 miles per week. The mean plasma midfollicular E2 values were 76% of the baseline values after a weekly mileage increase of 30 mi/wk and 48% at 50 mi/wk (2-sided P=0.03). However, Prg values were not obtained during the test cycles, and it is, therefore, unclear as to whether the E2 values reported occurred within ovulatory cycles.

In a study by Bullen et al. [13], 7 young women with prior athletic experience were trained at a high-intensity. The training protocol consisted of cycle ergometry 2 days/wk and running 4 days/wk at exercise intensities eliciting 85% of maximum heart rate. The duration of high-intensity activity was increased weekly from 20 mins/session to 45 mins/session over a 4 week period. Subjects trained at 45 mins/session for the remaining 4 weeks of the study. All of the cycles appeared to have been ovulatory, as evidenced by midcycle surges of LH and follicle stimulating hormone (FSH). Diminished urinary estriol (E3) levels were observed in 57% (4 of 7 subjects). Serum E2 levels were reported to have not changes appreciably, however no quantitative values were offered in the published report.

In a subsequent study of Bullen et al. [14], 28 initially untrained women with documented ovulation (urinary LH surge) were studied to determine whether strenuous exercise spanning two menstrual cycles would induce menstrual disorders. Initially, subjects ran 4 mi/day and increased

their training regimen to 10 mi/day by the end of week 5 and continued to run 10 mi/day for the remaining 5 weeks of the study. Subjects ran at 75% to 80% of maximum heart rate. Only 4 of 28 subjects (14%) had a normal cycle during one or both periods of exercise training. The criterion for normalcy included "a biphasic temperature curve, an ovulatory pattern of changes in gonadotropin and sex steroid excretion, and normal luteal function, defined as excretion of free Prg in a characteristic parabolic curve between the LH surge and beginning of the following menses". Keizer et al [15] assessed the effect of a 12 week endurance training program on plasma hormone responses among 8 previously untrained women. The training program consisted of running (2-3 times/week) and cycling (once/week). The training volume and intensity was progressively increased from a mean running speed of 9 km/hr (approx. 60% VO_2 max, equivalent to 65% of maximum heart rate [16]) and 20 min/day to 11-12 km/hr (approx. 80-85% of maximum heart rate) and 50-75 min/day. After training, follicular E2 values were 58% higher. However, the mean E2 value in the luteal phase was 57% (2-sided $P<0.01$) of the pre-training value. All subjects were reported to have ovulated in the pre-training test cycle. Based on pre- and post-training levels of Prg in the luteal phase (22.3 +/- 4.9 nmol/l, 20.8 +/- 0.4 nmol, respectively), all subjects were reported to have ovulated post-training, however, individual values were not reported and the data remain inconclusive. It is unclear to the reader as to when post-test measurements were obtained. If measurements were made appreciably after the cessation of the training program, effects of de-training may be present and this may explain, in part, the unremarkable findings of Keizer et al. [15]. The small sample size utilized in this study may have also contributed to the contrary findings of Bullen et al. [13,14].

In summary, there is some evidence to suggest that high intensity exercise training programs alter ovarian function and are in argument with cross-sectional studies. There have been no reported studies which assess the effect of a moderate *intensity* exercise training program on ovarian function in previously sedentary women. Moderate exercise intensity has been clearly defined by Pollack and his colleagues [16] who reported exercise intensities of 70% of maximum heart rate (approx. 80% of VO_2 max) as moderate in exertion.

In this proposal, we are conducting a modified version of the above described studies by integrating elements of each study to meet our standards of a moderate intensity exercise training program in which previously inactive women can reasonably be expected to partake in. We are enrolling each subject in a 6 month moderate exercise training program. Developing a long-term exercise training program allows us to assess the chronic effects of a moderate intensity exercise program on ovarian function. Furthermore, are expecting to utilize a substantially larger sample size than has been previously reported by other training studies. We have restricted the protocol to aerobic exercise training exclusively. This restriction will allow us to standardize the form and intensity of exercise for all subjects. We are able to monitor each participant and adjust their workload to maintain a previously set training level (see Methods). We will be able to assess the specific effects of aerobic activity with changes in E2 and Prg. In addition to determining changes in ovarian hormone levels, we will assess changes in luteal phase length and frequency of anovulation. These latter parameters have not been assessed in a prospective training study and will add significantly to our understanding of the effects of *moderate* exercise on ovarian function.

BODY

Hypotheses

The hypotheses of this study are:

1) Frequency of ovulation will be reduced as a result of a 6 month aerobic exercise training program of moderate intensity.
2) Serum Estradiol (E2) levels will be lower as a result of a 6 month aerobic exercise training program of moderate intensity.

3) Luteal phase menstrual cycle lengths will be shorter as a result of a 6 month aerobic exercise training program of moderate intensity.

Procedures

A prospective study has been undertaken to assess the effect of a 6 month moderate intensity exercise training program on basal hormonal levels among previously sedentary premenopausal women. In this study, we are, over a 3-year period, collecting blood and urine specimens (baseline and near the end of the 6 month training program) and questionnaire data from 120 women who agree to participate in exercise training program.

Subject Selection

Interested female participants are asked to complete a brief screening survey. The screening survey is intended to identify subjects who meet our criteria of inclusion. All study participants must meet the following criteria:

* nulliparous
* 18 to 35 years of age
* free of underlying diseases or conditions that may interfere with the measurement of hormone levels and/or the interpretation of hormone data
* have not used hormonal contraceptives over the past six months and not planning to over the course of participation in the study
* average menstrual cycle length between 15 and 45 days
* no regular exercise over the past 6 months
* BMI value between 20 and 30 kg/m^2
* no dieting over the past 6 months
* no smoking over the past 6 months

These criteria are set to reduce the impact of confounding variables which may be associated with altered ovarian function. We contact all interested women and review the responses provided on the screening survey to confirm eligibility. We then ask selected participants to notify us of the first day of their next menstrual cycle. At that time, subjects are asked to meet with us at a specified location, at a mutually convenient time to sign to an Informed Consent, to pick up a study kit, and to receive the questionnaire (described below).

Training Protocol:

A 6-month endurance training program at the Spectrum Club Manhattan Beach and the downtown YMCA is currently underway. We have chosen to conduct this training program over an extended period of time in an effort to determine the effects of a long-term exercise training program of moderate intensity on ovarian function, the effects of which are presently unknown. Subjects report to the study site and engage in a monitored aerobic exercise training program (weight lifting or cross training are not incorporated into the exercise prescription) for a total of 3 hours per week. The participants begin their training at 50% of their maximum heart rate for 20 minutes per session. Their training regimen is increased gradually to 60 minutes per session while they are at 65% of their maximum heart rate (see Table II).

Table I - Protocol for Individual Participation	
Study Months	Activity
1	Baseline hormone measurements
3-4	Training program begins and build up to 3 hrs/wk 65% maximum heart rate.
5-7	Maintain training at 4 at 3 hrs/wk hour per at 65% maximum heart rate
7	Comparative hormone measurements.

Table II - Training Protocol			
Week	Time (min)	% max. heart rate	% VO2 max.
1	20	50	40
2	20	50	40
3	20	60	45
4	30	60	45
5	30	65	50
6	40	65	50
7	50	65	50
8	60	65	50

Over the last 4 months of the study, each subject will be exercising for an hour each session about 65% of their maximum heart rate. This will be equivalent to 50% of their VO_2 max [16]. Corresponding heart rates will be calculated. Since training effects are expected to occur over the 6 month time period, staff will assist participants in adjusting their exercise protocol to coincide with 65% of their maximum heart rate.

Data Collection:

Baseline and Post-Training Testing:

(Per individual subject, based on an average cycle length of 28 days, longer cycles will require a slightly longer pre- and post-testing period.)

We take baseline measurements of weight, height, and VO_2 max (described below). These procedures must be completed by day 8 of the menstrual cycle (day 1 is the first day of the menses). We conduct baseline physiological test prior to the 6th month training program (month 1) and will repeat these measurements during the last month of the training period (month 7) to determine whether differences in hormone levels and frequency of ovulation exist.

Height and weight (month 1 and 7): These measurements are made at the time each participant is scheduled to pick-up her study kit (prior to the start of the study and near the end of exercise training program). Subjects are measured individually, out of the view of other subjects. Subjects are weighed without shoes or oversweaters. A Gopher G82-419 weigh balance scale is used to weigh each subject. The scale is re-calibrated daily. Measurement of height is performed immediately after weighing, and is done without shoes. A rigid measuring stick, calibrated in inches, is taped to the wall of the laboratory and the subject is asked to face forward with the back of her head against the stick. A ruler is then placed on top of the subject's head and the height read from the measuring tape on the wall. Dr. Shames along with the research assistants perform all measurements.

Questionnaire (month 1): Each participant completes a structured questionnaire that was designed by combining questionnaires developed by Dr. Bernstein in her previous studies of exercise activity and risk of breast cancer, and of the effect of exercise activity on menstrual patterns in adolescents, as well as questionnaires developed by Dr. Paffenbarger and his colleagues on physical activity [17-19], and Dr. Willett and his colleagues on diet [20-22]. It is important to collect detailed information on past exercise and dietary patterns since these may potentially influence the outcome measurements of this study. The proposed main study questionnaire will includes basic

demographic questions (age, race and socio-economic class based on education of parents), age at mearche, family history of cancer, and use of tobacco and alcohol. We are collecting this additional information to be used as covariates in future analyses regarding the effects of an exercise training program on ovarian function.

Diet will be assessed with a slightly modified version of the Semiquantitative Food Frequency Questionnaire (SFFQ) developed and validated by Dr. W. Willett and his colleagues [20-22]. The SFFQ was designed with the objective of categorizing individuals by their intake of nutrients hypothesized to affect the occurrences of cancer and heart disease. In its original form, the SFFQ consists of a 4-page printed Diet Assessment which can be mailed to subjects, and, when coded in pencil, provides machine-readable data. This form asks respondents how often they usually consumed a specified portion of 116 foods and drinks (over the previous year). with 9 response categories ranging from less than once a month to 6 or more servings per day. Additional items not presented in the food frequency form include the types of fat used for frying and cooking, the type of margarine used, the amounts of bran and sugar added to food, usual brands of cold breakfast cereal, frequency and brand of multiple vitamin supplements and the doses, iron, zinc, and calcium. We have modified the original questionnaire in consultation with Dr. Willett by adding a list of 24 additional foods, which have been utilized in funded case-control studies of endometrial (R01-CA48774-05) and ovarian (R01-CA61132-02S1) cancer in our department. The main aim of collecting these data will be to investigate whether diet is a confounder of any effects found with exercise.

Daily Records and Menstrual Calendars (months 1-7): We will be recruiting sedentary subjects, we will require that they avoid making any changes in lifestyle habits (e.g. diet, smoking, drinking and exercise --aside from the training study). However, some occasional recreational or other activity may occur. For this reason, they will record all physical activities over the previous 24 hours not included in the training program (i.e., recreational activity, occupational activity and daily routine) in daily logs over the entire study. Additionally, participants will be asked to maintain menstrual cycle calendars over the duration of the study. These calendars will be included in the study kit. On the calendar, each participant will record each day of menstrual bleeding for each menstrual cycle that occurs by circling the appropriate dates. These calendars are used to determine menstrual cycle lengths and to monitor menstrual cycle frequency over the duration of the study. Attendance and activity at the gym of each participant will be electronically monitored with a membership ID at the front desk and recorded by a member of our research team.

Heart Rates: During the course of the 6 months training program, heart rates will be monitored by two research assistants hired to aid and support participants while exercising. Subjects will wear an electrode chest belt with a corresponding wrist display to allow continuous monitoring of heart rate. This will alert the assistants to necessary changes in workloads so that subjects may maintain their exercise level at 65% of their maximum heart rate.

Biological Collections:

Biological specimens (urine and blood) are collected at baseline (month 1) and during the final month of training (month 7).

Urine collection: During the test menstrual cycle, daily urine samples beginning on cycle day 10 and continuing until the first day of the second cycle will be collected from each participant. Plastic bottles for urine collection will be provided. Accompanying the bottles is a list of directions instructioning the subject that we wish to collect a 30 ml sample of first morning urine and

specifying procedures to follow. We monitor each participants progress and make intermittent reminder phone calls to follow-up on the study protocol and answer any questions that may have arisen. Subjects will notify us as to the start of their next menstrual cycle and this date signifies the completion of the biological collections. Each participant will be telephoned the night prior to the first scheduled urine collection in each cycle as a reminder, and to answer any questions they may have regarding urine collection. Once a week, participants will asked to bring the daily urine specimens in a freezer lunch bag with frozen blue ice (supplied in the kit) to drop off at the study site refrigerator. Samples will be picked up daily by Dr. Shames or a research assistant and stored on the medical campus at -86°C until analyzed.

Each day's collection for each subject is identified by a 6 digit ID (xxx-xx-x) and date of urine collection. The first 3 digits of the ID represent the student's unique ID number (001-300) and will be assigned chronologically at the time of enrollment. Digits 4 and 5 represent the day of the menstrual cycle for the particular sample. The final digit is the cycle number.

Serum collection: Subjects will be asked to provide from 2 to 5, 15 ml blood samples (depending on the length of their cycle). Blood will be taken at the study site on cycle days 11 (±1) and 22 (±1) [and subsequently on days 29 (±1), 36 (±1) 43 (±1), in the event menses has not occurred]. Most subjects will provide 2 or 3 samples. We allow a one day variation to account for samples which may fall on a weekend and for unavoidable conflicts. Subjects report to the gym between 7:30 AM and 9:30 AM (on the day of their scheduled appointment) in a fasting state and have refrained from exercise activities for at least 5 hours. Each subject is contacted the evening prior to their appointments as a reminder. Blood specimens will be processed into serum and stored at -86°C for analysis. Sterile 2 ml polypropylene low temperature freezer vials are coded with the same 6 digit coding system as described above for urine, plus an additional digit for aliquot number.

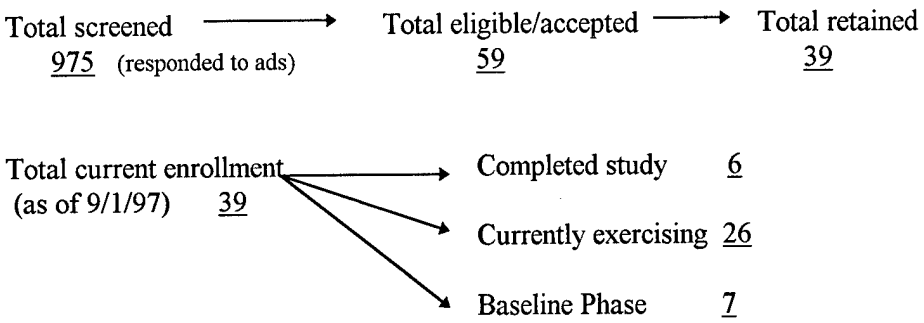
Progress (Year 1):

We have devoted an enormous amount of time and effort in year 1 to the advertisement and recruitment for this study. As indicated above, our study criteria is quite rigorous and only very select women meet these criteria (see chart, next page).

We began our recruitment efforts by placing fliers within a three mile radius of the designated study site. We placed fliers at grocery stores, video stores, movie theaters, shopping malls and various other local shops. Additionally, we attended local health and community fairs and posted signs in several of the larger engineering and computer firms (e.g., Xerox, TRW, Hughes Aircraft, Mattel, Aerospace).

As a study incentive, we arranged to provide a 6 month health club membership at the Spectrum Club in Manhattan Beach at no cost to the subject ($600 retail value). At the end of the training study, each participant that completes the study receives a reduced membership rate to continue use of these facilitates and is compensated with $160.00 for their time, effort and transportation costs.

Year 1 participation statistics:



The training protocol has remained essentially unchanged. However, in order to fully engage women in their exercise activities, and to prevent high study attrition rates we offered subjects other forms of aerobic activity such as the treadmill and stairmaster as well as the stationary bicycle. Frequency, intensity and duration of these activities has not been altered. In order to compensate for any emergency absences, we lengthen the program to correspond to the amount of time away from the study. We will analyze our laboratory specimens in groups of 10 as subjects complete the study.

Recruitment (Year 2):

We have enhanced our strategy for recruitment during the second year of this study. We began placing ads in the health and calendar sections of local newspapers and cable television stations to increase our range of exposure. We have secured spots on 4 area cable stations and 9 newspapers covering a range from as far east as Pasadena, traveling west through Santa Monica, and as far south as Redondo Beach. Additionally, we have added a second study site (in metropolitan Los Angeles area) to access women throughout the southland who may work or live near the downtown area. We have been featured in the Downtown News, participated in a Los Angeles business area health fair, and will be speaking to several of the large businesses in the area.

Data Management:

The day-to-day tracking of participants has been managed on an IBM compatible PC using d-Base. Using this database, we can effectively monitor participants accrual, assessment responses, gym attendance and track all data collection throughout the study (i.e., questionnaire data, physical measurements, daily physical activity logs, urine and serum collection appointments, etc.).

Both the initial screening questionnaire and the study questionnaire have been coded and readied for data entry. Height, weight, body fat measurements, and VO2 max (pre - and post-training) have been coded. The completed Diet Assessments will be checked for stray marks and completeness of coding and sent to Dr. Willett for analysis. Dr. Willett's nutritionist team will also code any additional foods from the 24-item Los Angeles supplement list and compute nutrient scores for total calories, saturated fat, polyunsaturated fat, cholesterol, other and both crude and dietary fiber. All items are coded using the coding system developed for the Nurses' Health Study [20-22]. At the end of each semester, Dr. Willett will send us a computer disk containing both the

raw food frequency data and the nutrient scores for all subjects. These will be merged with the remainder of our data.

Data are entered as the study progresses on an IBM compatible personal computer and files are backed-up on floppy disks. Interactive data editing procedures will be used to edit data. Ranges of values will be checked for each variable. A series of consistency checks will be performed. Inconsistencies will be resolved by re-contacting the subject. Computer-generated individualized diet assessments will be returned, and mailed to study subjects alone with an explanatory leaflet as a token of our appreciation for the cooperation.

We will strictly maintain the confidentiality of data through use of locked cabinets accessible only to employees directly involved in the study who have signed an employee confidentiality form. Computer-stored information will have only the study identification number to insure security. We will publish results from the study in a tabular descriptions of groups or in a form which precludes identification of specific individuals.

CONCLUSIONS

The analysis phase of this study will commence in mid-November 1997.

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